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EXAMINER	
RAE, CHARLESWORTH E	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/685,942	Applicant(s) MAN ET AL.	
	Examiner Charleswort Rae	Art Unit 1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 July 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 5* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgement is made of applicants' filing of the instant application, filed 7/20/07, as a Request for Continued Examination (RCE) under 37 CFR 1.1114. The Notice of Appeal, filed 4/24/07, is rendered moot by the filing of the instant application.

Applicant's arguments and accompanying **Exhibit A** (i.e. *In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995*))* have been fully considered but they are not deemed to be persuasive.

This action is made final.

Status of the Claims

Claims 1 and 5 are currently pending in this application.

Summary of Response to Arguments

Obviousness-Type Double Patenting (ODP) rejection (claims 1 and 5)

With respect to the judicially created Obviousness-Type Double Patenting (ODP) rejection of claims 1 and 5 over claim 14 of U.S. Patent 6,667,316 ('316 patent'), made in the Office action mailed 01/24/07 (see pages 2-5), applicant traverses on the grounds that this rejection should be withdrawn because the Examiner's use of the '316 specification is improper. Applicant contends that the term **"undersirable angiogenesis"** as recited in claim 14 of the '316 patent' does NOT encompass the reduction of PDE IV level or the treatment of inflammatory or autoimmune diseases because the specification clearly provides that "method of inhibiting PDE IV," "method of treating undesirable angiogenesis," "method of treating inflammatory disease" and "method of treating autoimmune disease" are individual and separate embodiment of this invention (paragraphs 2-3, on page 1 of applicant's Response of 04/24/07). This argument is not deemed persuasive, however, as the interpretation of the term **"undersirable angiogenesis"** as recited in claim 14 of the '316 patent must be construed in light of the specification of the '316 patent and NOT in light of the instant specification as applicant contends.

Second, applicant contends that assuming, arguendo, that the portions referred to by the Examiner could provide a basis for the ODP rejection, those portions, when considered in combination with claim 14 of the '316 patent, cannot render the pending claims obvious because, even if taken true, as such a proposition does NOT support the Examiner's conclusion that the term **"unregulated angiogenesis"** encompasses "inflammatory or autoimmune disease and ... the limitation of reducing elevated levels of PDE IV as being an attendant effect or necessary correlate thereof (page 2, second to last line to page 3, page 10, of applicant's above-referenced Response). Applicant asserts that this is because, for example, those skilled in the art would NOT have had a reasonable expectation of successfully "treating inflammatory or autoimmune disease" or "reducing the level of PDE IV" using a compound, even if it was known that such a compound is effective in treating the diseases recited by the definition provided by the Examiner; and NO evidence, in the '316 specification or in the prior art, is provided by the Examiner to support the proposition. This argument is also not deemed persuasive as the use of the specification in an ODP analysis is limited only to its use as a "dictionary." Besides, the '319 patent is presumed to be valid and therefore enabling for the subject matter as claimed in reference claim 14.

For these reasons and for the reasons previously made of record, this rejection is maintained.

Enablement rejection under 112, first paragraph

With respect to the 35 USC 112, first paragraph, rejection of claims 1 and 5, made in the above referenced Office action (see pages 5-13), applicant contends that

1) Bielekova et al. (reference already made of record) as cited by the Examiner does not provide a proper **"reason to doubt"** the statements made in the instant specification in view of *In re Brana **(Exhibit A)*** wherein the facts are virtually identical to those in the instant application (Applicant's Response, page 3, last paragraph to page 4, last full paragraph).

2) If any experimentation is required to make and use the instant claimed methods, such experimentation would not be undue (Applicant's Response, page 4, second to last sentence to page 5, second to last paragraph).

Applicant's analysis of *In re Brana*, as set forth below:

> In *Brana*, the examiner rejected claims to "anti-cancer" use of certain compounds based on prior art references which reportedly disclosed mouse models for assessing anti-tumor activity (which was used by the applicants in their specification) may not be indicative of the test compounds' therapeutic value in humans. (*Id.* at 1565-6). However, the court held that the examiner has failed to meet her initial burden of establishing that the presumption of enablement is rebutted because the references provided by the examiner "do not question the usefulness of any compound as an antitumor agent or provide any other evidence to cause one of skill in the art to question the asserted utility of applicants' compounds." (*Id.* at 1566) (emphasis added). Further, the court held that "[the] references merely discuss the therapeutic predictive value of in vivo murine test," but such disclosure is relevant "only if applicants must prove the ultimate value in humans of their asserted utility," indicating that such proof of "ultimate value in humans" cannot be required in assessing patentability. (*Id.*) (emphasis added).
>
> Like in *Brana*, the Examiner provides essentially the same piece of disclosure in this application, *i.e.*, a reference that states in a very general term that animal test results may not be indicative of a compound's therapeutic value in humans. Therefore, because such a showing is not sufficient to "cause one of skill in the art to question the asserted utility of Applicants' compounds," and because Applicants are not required to "prove the ultimate value in humans" of the compounds recited by the pending claims, Applicants respectfully point out that the rejection of the claims under 35 U.S.C. § 112 cannot stand.

Contrary to applicant's statement that the facts in *Brana* are virtually identical to those in the instant case, the facts of the instant case are considered to be clearly distinguishable from those in *Brana*. First, the issue of law raised in *Brana* was whether "asserted utility" was a proper test for determining enablement under 112, first paragraph. No issue of "asserted utility" are present in the instant case and there is no requirement that is being made of applicant to prove the ultimate value in humans. The basis inquiry in this case is whether the instant disclosure teaches those skilled in the art how to make and use the instant invention commensurate with the full scope of the claimed invention without undue experimentation.

Second, the facts at issue in Brana are also distinguishable from the facts of the instant case. In the instant case, the claims are very broad and encompass a diverse group of inflammatory and autoimmune diseases that are characterized by different immunopathologies, etiologies, and clinical manifestations as evidenced by the teaching of Harrison's textbook (Harrison's Principles of Internal Medicine (1994), pages 1543-1566; see specifically Tables 277-1 and 277-2). Unlike in *Brana*, wherein a well-recognized mouse model was used to determine the anti-cancer activity of the compounds against specific species of cancer, no *in vitro* model is well recognized in the art for reliably and predictably determining the anti-PDE IV activity of the instant claimed compounds against a specific disease species or the genus of inflammatory and autoimmune diseases. Furthermore, the art teaches that PDE IV and PDE III etc. exert complex immunomodulatory effects and raises doubts regarding whether the concentration of PDE inhibitors necessary to inhibit PDE levels *in vitro* models can be extrapolated to *in vivo* systems i.e. humans. To reiterate (see Office action mailed 01/24/07, pages 8-10),

> **In particular, Bielekova et al. disclose that hyperactive Th1-mediated immune responses are thought to be involved in the pathogenesis of many autoimmune**

diseases (Bielekova et al. Therapeutic potential of phosphodiesterase-4 and 3-inhibitors in Th1-mediated autoimmune diseases. The Journal of Immunology, 2000, 164:1117-1124, see page 1117, column 1, lines 1-3). Immune cells predominantly express families PDE 4, PDE3, and, to a lesser extent, PDE7 (page 1117, column 1, lines 6-8). Inhibitors of PDE4 and PDE3 families exert complex immunomodulatory properties (page 1117, column 1, lines 8-10). In animals, these drugs inhibit Ag-mediated T cell proliferation and skew the T cell cytokine profile toward a Th2 phenotype by down-regulating the expression or production of Th1 cytokines and have no effect or even augment the production of Th2 cytokines (page 1117, column 1, lines 10-14). These properties render PDE inhibition a candidate therapy for Th1-mediated autoimmune disorders (page 1117, column 1, lines 14-16). Bielekova et al. further disclose that the **simple extrapolation of therapeutic efficacy from animal models to human disorders is not easily feasible** ... (page 1117, column 1, lines 19-23). Although there is some evidence for a preferential inhibition of proinflammatory cytokines in Th1-mediated human autoimmune conditions, data from asthmatic and atopic individuals reached almost opposite conclusion (page 1117, column 2, lines 2-7). Bielekova et al. disclose that the question remains of whether the immunomodulatory effect of PDE IV inhibitors is expressed within a concentration range that is achievable in humans in vivo (page 1123, column 1, last paragraph, lines 1-5). Well designed therapeutic trials supported by immunological studies should not only provide more definite information about the therapeutic potential of PDE inhibitors in autoimmune disorders, but also broaden our understanding of the immunopathogenesis and the

potentail differences among individual human TH1-mediated autoimmune diseases (page 1123, column 2, last paragraph).

Rejections

Nonstatutory Obviousness-Type Double-Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1 and 5 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 14, in view of claims 1-2, 12-13, and 16-17 of U.S. Patent 6,667,316 ('316). Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are either anticipated by, or would have been obvious in view of the referenced claims.

The above discussion of the ODP rejection in connection with the Response to applicant's arguments is incorporated by reference.

In particular, claim 14 of Man '316 recites a method for treating undesirable angiogenesis which comprises administering thereto an effective amount of a substantially chirally pure (R)- or (S)-isomer of a compound according to claim 1 that upon administration in a single or multiple dose regimen is pharmaceutically effective and ii) a pharmaceutically acceptable carrier thereof. Unlike the claims of the instant application, the method of said reference claim 14 does not recite the intended use as "***[a] method of reducing elevated levels of PDE IV in mammal***," as in the case of instant claim 1, or the intended use as "***[a] method of treating an inflammatory disease or an autoimmune disease in a mammal***," as in the case of instant claim 5. To the extent that reference claim 14 does not recite these necessary limitations to practice the invention as claimed, it is reasonable to look towards the specification as a “dictionary” to determine the meaning of the term “undesirable angiogenesis” (see MPEP 804).

The term “unregulated angiogenesis” is defined by the reference specification as being “pathologic and sustains progression of many neoplastic and non-neoplastic diseases including solid tumor growth and metastases, arthritis, some types of eye disorders, and psoriasis (‘316, specification, column 2, lines 1-4). This term “unregulated angiogenesis” given its broadest reasonable interpretation in view of the specification can reasonably be construed as meaning “undersirable angiogenesis.” Thus, it is reasonable to construe the limitation “unregulated angiogenesis” to encompass inflammatory or autoimmune disease and to construe the limitation of “reducing elevated levels of PDE IV” as being an attendant effect or necessary correlate of treating inflammatory or autoimmune diseases with compounds encompassed by reference claim 14 (‘316, specification, column 5, lines 24-28).

Thus, the instant claims are obvious variants of the absent limitations of the referenced claims because a method of treating undesirable angiogenesis comprising administering an effective amount of a substantially chirally pure (R)- or (S)-isomer of a compound according to claim 1 that upon administration in a single or multiple dose regimen is pharmaceutically effective and ii) a pharmaceutically acceptable carrier thereof, necessarily encompasses the ***method of reducing elevated levels of PDE IV in mammal / method of treating an inflammatory disease or an autoimmune disease in a mammal***, comprising administering an effective amount of cyclopropyl-N-

{2-[1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-3-oxoisoindolin-4-yl}carboxamide, or an acid addition salt or a substantially pure isomer.

Thus, claims 1 and 5 are deemed to be obvious variants of the limitations of the patented subject matter claimed in Han '316.

Claim Rejections – 35 USC 112 – First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 5 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate with the full scope of the claims. This is a scope of enablement rejection.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fd. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

The test is not merely quantitative, since a considerable amount of experimentation is permissible, if its is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth in *In re Wands,* 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman* 230 USPQ 546 (BdApls 1986) at 547 the court cited eight factors:

1) the quantity of experimentation necessary,
2) the amount of direction or guidance provided,
3) the presence or absence of working examples,
4) the nature of the invention,
5) the state of the prior art,
6) the relative skill of those in the art,
7) the predictability of the art, and
8) the breadth of the claims

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the Wands factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill of those in the art.

The invention in general is directed towards a method of reducing elevated levels of PDE IV (claim 1), and a method of treating an inflammatory or an autoimmune disease (claim 5), in a mammal, comprising administering an effective amount of a compound of formula I or an acid addition salt or a substantially chirally pure isomer thereof. The relative skill of those in the art is high, generally that of an M.D. or Ph.D. It is noted that the pharmaceutical art is generally unpredictable, requiring each embodiment to be individually assessed for therapeutic activity. The more unpredictable an area, the more specific enablement is necessary in order to satisfy the statue. (see *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970)). For example, the mode of action of immunomodulatory agents is often unknown or very unpredictable and administration of such agents is often accompanied by undersirable effects. The immunopathogenesis of inflammatory and autoimmune diseases is considered to be very complex and varies widely, depending on the particular inflammatory or autoimmune disease. The therapeutic modalities also vary widely depending on the particular inflammatory or autoimmune disease. Besides, there is a disproportionately sparse number of discovery of new and predictable treatments for inflammatory and autoimmune diseases compared with the vast number of new drugs discovered.

The above discussion of the enablement rejection in connection with the Response to applicant's arguments is incorporated by reference.

The specification of the instant application discloses that it is recognized that the inhibition of PDE type IV is particularly effective in both the inhibition of inflammatory mediator release and the relaxation of airway smooth muscle and that compounds that inhibit PDE IV specifically, would exhibit the desirable inhibition of inflammation and relaxation of airway smooth muscle with a minimum of unwanted side effects, such as cardiovascular or anti-platelet effects (page 9, lines 15-22). Applicant further discloses that currently used PDE IV inhibitors lack the selective action at acceptable therapeutic doses. Applicant asserts that compounds of the instant invention are useful in the inhibition of phosphodiesterase, particularly PDE II and PDE IV, and in the treatment of disease states mediated thereby, including inflammatory, infectious, immunological and malignant diseases (page 9, line 22 to page 10, line 9).

Also, applicant discloses a number of methods for preparing the instant compounds of formula I (page 13, line 15 to page 20, line 16). Applicant discloses that the compounds possess a center of chirality and thus can exist as optical isomers (page 20, lines 17-18). Applicant also discloses that inhibition of PDE III, PDE IV, TNFα and NFκB by the instant compounds of general formula I can be conveniently assayed by using methods known in the art (page 21, lines 4-7). Applicant discloses various methods of treatment by administering to a mammal an effective amount of a substantially chirally pure ®- or (S)-isomer of a compound of instant formula I or a mixture of those isomers (page 24, 10-23). Applicant further discloses that while these treatment methods may overlap, they also may differ in terms of method of administration, dose level, dosage regimen (such as single or multiple doses), and concurrently administered therapeutic agents (page 24, lines 23-26).

As applicant states in the response filed June 28, 2006, that "a specification disclosure ... must be taken as being in compliance with the enablement requirement ... unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." In the instant case, there is reason to doubt the objective truth of the statements contained in the specification.

In particular, Bielekova et al. disclose that hyperactive Th1-mediated immune responses are thought to be involved in the pathogenesis of many autoimmune diseases (Bielekova et al. Therapeutic potential of phosphodiesterase-4 and 3-inhibitors in Th1-mediated autoimmune diseases. The Journal of Immunology, 2000, 164:1117-1124, see page 1117, column 1, lines 1-3). Immune cells predominantly express families PDE 4, PDE3, and, to a lesser extent, PDE7 (page 1117, column 1, lines 6-8). Inhibitors of PDE4 and PDE3 families exert complex immunomodulatory properties (page 1117, column 1, lines 8-10). In animals, these drugs inhibit Ag-mediated T cell proliferation and skew the T cell cytokine profile toward a Th2 phenotype by down-regulating the expression or production of Th1 cytokines and have no effect or even augment the production of Th2 cytokines (page 1117, column 1, lines 10-14). These properties render PDE inhibition a candidate therapy for Th1-mediated autoimmune disorders (page 1117, column 1, lines 14-16). Bielekova et al. further disclose that the **simple extrapolation of therapeutic efficacy from animal models to human disorders is not easily feasible** ... (page 1117, column 1, lines 19-23).

Although there is some evidence for a preferential inhibition of proinflammatory cytokines in Th1-mediated human autoimmune conditions, data from asthmatic and atopic individuals reached almost opposite conclusion (page 1117, column 2, lines 2-7). Bielekova et al. disclose that the question remains of whether the immunomodulatory effect of PDE IV inhibitors is expressed within a concentration range that is achievable in humans in vivo (page 1123, column 1, last paragraph, lines 1-5). Well designed therapeutic trials supported by immunological studies should not only provide more definite information about the therapeutic potential of PDE inhibitors in autoimmune disorders, but also broaden our understanding of the immunopathogenesis and the potentail differences among individual human TH1-mediated autoimmune diseases (page 1123, column 2, last paragraph).

The unpredictability or uncertainty in the art is illustrated by the fact that there is some evidence to show a preferential inhibition of proinflammatory cytokines in Th1-mediated human autoimmune conditions, data from asthmatic and atopic individuals reached almost opposite conclusion (Buelekova et al., page 1117, column 2, lines 2-7). Thus, one skilled in the art would not be able to predictably extrapolate the disclosed teachings of the claimed invention to inflammatory and autoimmune diseases with any reasonable degree of certainty.

The breadth of the claims

The claims are very broad. For example, claims 1 encompasses all mammalian species, multiple variants of the elected compound, cyclopropyl-N-{2-[1(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-3-oxoisindolin-4-yl}carboxamide, various diverse conditions involving unregulated angiogenesis, including a heterogenous group of inflammatory and autoimmune diseases that are characterized by different immunopathologies and etiologies. Because the therapeutic response to be achieved would necessarily vary depending upon the specific inflammatory or autoimmune disease that is intended to be treated, the level of predictably in practicing the claimed invention would be greatly diminished.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides limited direction or guidance for determining the particular administration regimens (dosages, timing, administration routes etc.) necessary to treat all inflammatory and autoimmune diseases associated with unregulated angiogenesis. The 'working examples" are limited to in vitro experiments. Thus, the applicant at best has provided specific direction or guidance only for an in vitro methodology for evaluating PDE IV inhibitory effects of the elected compound of instant general formula I. No reasonably specific guidance is provided concerning useful therapeutic protocols for treating inflammatory and autoimmune diseases.

4. The quantity of experimentation necessary

In view of applicant's disclosure that the treatment methods while they may overlap, they also may differ in terms of method of administration, dose level, dosage regimen (such as single or multiple doses), coupled with the complex and different immunopathologies associated with inflammatory and autoimmune diseases (page 24, lines 23-26), it is reasonable to surmise that this level of uncertainty and unpredictability in the art would require one skilled in the art to conduct more than routine experimentation in order to practice the claimed invention as claimed.

For the reasons stated above, claims 1 and 5 are rejected under 35 USC 112, first paragraph, for lack of enablement because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention as claimed.

No claims allowed.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

This is a Request for Continued Examination (RCE) of applicant's earlier Application No. 10/685,942. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Charlesworth Rae whose telephone number is 571-272-6029. The examiner can normally be reached between 9 a.m. to 5:30 p.m. Monday to Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached at 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http:pair-direct.uspto.gov. Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 800-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

BRIAN-YONG S. KWON
PRIMARY EXAMINER